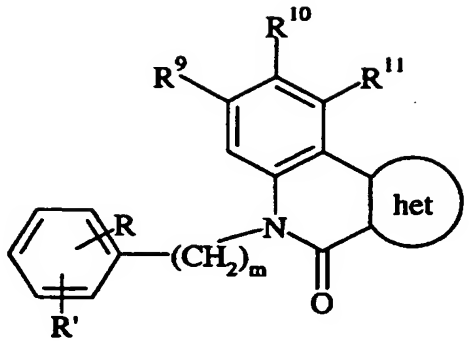
We Claim:

1. A compound of formula I:



I

where:

het is a five (5) membered heteroaryl ring containing N and a second heteroatom selected from N, O, or S;

wherein the non-fused carbon atom of the heteroaryl ring is optionally substituted with C_1-C_6 alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, an amino acid ester, CH_2OH, CH_2O-heterocycle, halo, CH_2N_3, CH_2SR^1, $CH_2NR^4R^5$, OR^1, SR^{12}, $S(CH_2)_n$-phenyl, or NR^4R^5; provided that when het is pyrazole or imidazole, the saturated nitrogen of the het ring is optionally substituted with C_1-C_4 alkyl;

R is $(CH_2)_m$'CHR^1NHR^2, $O(CH_2)_2NHR^2$, $(CH_2)_m$'COR^3, NHR^2, and $(CH_2)_m$'$CHR^1NR^4R^5$;

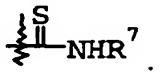
R' is hydrogen, hydroxy, or O(C_1-C_6 alkyl optionally substituted with phenyl or C_3-C_7 cycloalkyl);

m and m' are independently at each occurrence 0, 1, or 2;

R^1 is independently at each occurrence hydrogen or C_1-C_6 alkyl;

Frequently, it will be desirable or necessary to introduce the pharmaceutical formulation to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions, which can transiently open the blood-brain barrier.

R^2 is hydrogen, COR^6, $CH_2R^{6'}$, SO_2R^7, or a moiety of the formula  ;

R^3 is hydrogen, hydroxy, C_1-C_6 alkoxy, an amino acid ester, an amino acid, or NR^4R^5;

R^4 is hydrogen or C_1-C_6 alkyl;

R^5 is hydrogen, C_1-C_6 alkyl, C_6-C_{10} bicycloalkyl, (C_1-C_4 alkyl)-phenyl, (C_1-C_4 alkyl)-CO_2R^1, $CH_2CO_2R^1$, aryl, substituted aryl, $(CH_2)_nCHR^8NHC(O)OC(CH_3)_3$, $(CH_2)_nNH_2$, $(CH_2)_2NHCOR^6$, $(CH_2)_2OR^1$, $(CH_2)_q$-heterocycle, $(CH_2)_q$-substituted heterocycle, or R^4 and R^5, together with the nitrogen to which they are attached, combine to form a pyrrolidin-1-yl, piperidin-1-yl, hexamethyleneimin-1-yl, or morpholin-4-yl ring;

n is 1, 2, 3, or 4;

q is 0, 1, 2, or 3;

R^6 is C_1-C_6 alkyl, substituted C_3-C_6 cycloalkyl, aryl, substituted aryl, *tert*-butoxy, $(CH_2)_q$-heterocycle, $(CH_2)_q$-substituted heterocycle, $(CH_2)_nS(O)_rR^1$, $C(CH_3)_2CH_2N(R^1)_2$, $(CH_2)_nCHR^8NHC(O)OC(CH_3)_3$, $(CH_2)_nCHR^8NH_2$, $(CH_2)_2NH$-aryl, or NHR^7;

$R^{6'}$ is C_1-C_6 alkyl, substituted C_3-C_6 cycloalkyl, aryl, substituted aryl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-substituted heterocycle, $(CH_2)_nS(O)_rR^1$, $C(CH_3)_2CH_2N(R^1)_2$, $(CH_2)_nCHR^8NH$-$C(O)OC(CH_3)_3$, $(CH_2)_nCHR^8NH_2$, or $(CH_2)_2NH$-aryl;

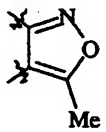
r is 0, 1, or 2;

R^7 is C_1-C_6 alkyl, phenyl, or substituted phenyl;

R^8 is hydrogen or CO_2R^1; and

R^9, R^{10}, and R^{11} are independently at each occurrence hydrogen, halo, CO_2R^1, aryl, substituted aryl, thiophene, C_1-C_4 alkoxy, (C_1-C_3 alkyl)-phenyl, or C_2-C_6 alkenyl;

R^{12} is C_1-C_6 alkyl, (C_1-C_4 alkyl)-phenyl, aryl, substituted aryl, heterocycle or substituted heterocycle; or

a pharmaceutical salt thereof; provided that if R^9 and R^{10} are hydrogen and R^{11} is chloro, then het is not  .

2. The compound according to Claim 1 where m is 0 and R is at the meta position.

3. The compound according to Claim 2 where R is $(CH_2)_{m'}CHR^1NHR^2$ and m' is 0 and R^1 is methyl.

4. The compound according to Claim 3 where R^2 is 3,4,5-trimethoxybenzyl.

5. The compound according to Claim 2 where R is $(CH_2)_{m'}COR^3$ and m' is 0 or 1.

6. The compound according to Claim 5 where R^3 is (3,4,5-trimethoxyphenyl)amino, (4-aminosulfonylphenyl)amino, or (6-methoxyquinolin-8-yl)amino.

7. The compound according to Claim 2 where R is $(CH_2)_{m'}CHR^1NR^4R^5$ and m' is 0, and R^1 and R^4 is hydrogen.

8. The compound according to Claim 7 where R^5 is 5-methylisoxazol-3-yl, 3,5-dimethoxy-4-hydroxybenzyl, or 3,4,5-trimethoxybenzyl.

9. A method of inhibiting MRP1 in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof.

10. The method according to Claim 9 where the mammal is a human.

11. The method according to Claim 10 where the compound of formula I is a compound where m is 0 and R is at the meta position.

12. The method according to Claim 11 where the compound of formula I is a compound where R is $(CH_2)_{m'}CHR^1NHR^2$ and m' is 0 and R^1 is methyl..

13. The method according to Claim 12 where the compound of formula I is a compound where R^2 is 3,4,5-trimethoxybenzyl.

14. The method according to Claim 11 where the compound of formula I is a compound where R is $(CH_2)_{m'}COR^3$ and m' is 0 or 1..

15. The method according to Claim 14 where the compound of formula I is a compound where R^3 is (3,4,5-trimethoxyphenyl)amino, (4-aminosulfonylphenyl)amino, or (6-methoxyquinolin-8-yl)amino.

16. The method according to Claim 11 where the compound of formula I is a compound where R is $(CH_2)_{m'}CHR^1NR^4R^5$ and m' is 0, and R^1 and R^4 is hydrogen.

17. The method according to Claim 16 where the compound of formula I is a compound where R^5 is 5-methylisoxazol-3-yl, 3,5-dimethoxy-4-hydroxybenzyl, or 3,4,5-trimethoxybenzyl.

18. A method of inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance, in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof; in combination with an effective amount of one or more oncolytic agents.

19. The method according to Claim 18 where the mammal is a human.

20. The method according to Claim 19 where the oncolytic(s) is selected from: doxorubicin, daunorubicin, epirubicin, vincristine, and etoposide.

21. The method according to Claim 19 where the neoplasm is of the Wilm's type, bladder, bone, breast, lung(small-cell), testis, or thyroid or the neoplasm is associated with acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphomas, and bronchogenic carcinoma.

22. The method according to Claim 19 where the compound of formula I is a compound where m is 0 and R is at the meta position.

23. The method according to Claim 22 where the compound of formula I is a compound where R is CHR^1NHR^2 and R^1 is methyl.

24. The method according to Claim 23 where the compound of formula I is a compound where R^2 is 3,4,5-trimethoxybenzyl.

25. The method according to Claim 22 where the compound of formula I is a compound where R is COR^3 or $(CH_2)COR^3$.

26. The method according to Claim 25 where the compound of formula I is a compound where R^3 is (3,4,5-trimethoxyphenyl)amino, (4-aminosulfonylphenyl)amino, or (6-methoxyquinolin-8-yl)amino.

27. The method according to Claim 22 where the compound of formula I is a compound where R is $(CH_2)NR^4R^5$ and R^4 is hydrogen.

28. The method according to Claim 27 where the compound of formula I is a compound where R^5 is 5-methylisoxazol-3-oyl, 3,5-dimethoxy-4-hydroxybenzyl, or 3,4,5-trimethoxybenzyl.

29. A pharmaceutical formulation comprising a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof; in combination with one or more pharmaceutical carriers, diluents, or excipients therefor.

30. A pharmaceutical formulation comprising:

(a) a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof;

(b) one or more oncolytic agents; and

(c) one or more pharmaceutical carriers, diluents, or excipients therefor.

31. The formulation according to Claim 30 where the oncolytic(s) is selected from: doxorubicin, daunorubicin, epirubicin, vincristine, and etoposide.

32. A use of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance in a mammal.

33. A use of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting MRP1.

34. A use of a compound of formula I, as defined in Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting MRP1 conferred MDR in a resistant neoplasm, or a neoplasm susceptible to resistance in a mammal.

35. A use of a compound of formula I, as defined in Claim 1, in therapy.

36. A pharmaceutical composition for inhibiting MRP1 in a mammal which comprises an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof.

37. The composition according to Claim 36 where the mammal is a human.

38. The composition according to Claim 37 where the compound of formula I is a compound where m is 0 and R is at the meta position.

39. The composition according to Claim 38 where the compound of formula I is a compound where R is $(CH_2)_{m'}CHR^1NHR^2$ and m' is 0 and R^1 is methyl..

40. The composition according to Claim 39 where the compound of formula I is a compound where R^2 is 3,4,5-trimethoxybenzyl.

41. The composition according to Claim 38 where the compound of formula I is a compound where R is $(CH_2)_{m'}COR^3$ and m' is 0 or 1..

42. The composition according to Claim 41 where the compound of formula I is a compound where R^3 is (3,4,5-trimethoxyphenyl)amino, (4-aminosulfonylphenyl)amino, or (6-methoxyquinolin-8-yl)amino.

43. The composition according to Claim 38 where the compound of formula I is a compound where R is $(CH_2)_{m'}CHR^1NR^4R^5$ and m' is 0, and R^1 and R^4 is hydrogen.

44. The composition according to Claim 43 where the compound of formula I is a compound where R^5 is 5-methylisoxazol-3-yl, 3,5-dimethoxy-4-hydroxybenzyl, or 3,4,5-trimethoxybenzyl.

45. A pharmaceutical composition for inhibiting a resistant neoplasm, or a neoplasm susceptible to resistance, in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of formula I, as defined in Claim 1, or a pharmaceutical salt thereof; in combination with an effective amount of one or more oncolytic agents.

46. The composition according to Claim 45 where the mammal is a human.

47. The composition according to Claim 46 where the oncolytic(s) is selected from: doxorubicin, daunorubicin, epirubicin, vincristine, and etoposide.

48. The composition according to Claim 46 where the neoplasm is of the Wilm's type, bladder, bone, breast, lung(small-cell), testis, or thyroid or the neoplasm is associated with acute lymphoblastic and myeloblastic leukemia, neuroblastoma, soft tissue sarcoma, Hodgkin's and non-Hodgkin's lymphomas, and bronchogenic carcinoma.

49. The composition according to Claim 46 where the compound of formula I is a compound where m is 0 and R is at the meta position.

50. The composition according to Claim 49 where the compound of formula I is a compound where R is CHR^1NHR^2 and R^1 is methyl.

51. The composition according to Claim 50 where the compound of formula I is a compound where R^2 is 3,4,5-trimethoxybenzyl.

52. The composition according to Claim 49 where the compound of formula I is a compound where R is COR^3 or $(CH_2)COR^3$.

53. The composition according to Claim 52 where the compound of formula I is a compound where R^3 is (3,4,5-trimethoxyphenyl)amino, (4-aminosulfonylphenyl)amino, or (6-methoxyquinolin-8-yl)amino.

54. The composition according to Claim 49 where the compound of formula I is a compound where R is $(CH_2)NR^4R^5$ and R^4 is hydrogen.

55. The composition according to Claim 54 where the compound of formula I is a compound where R^5 is 5-methylisoxazol-3-oyl, 3,5-dimethoxy-4-hydroxybenzyl, or 3,4,5-trimethoxybenzyl.